Amendments to the Specification:

Please replace the paragraph [0037] with the following amended paragraph(s):

[0037] The term "ligand" refers to a molecule that is or that can be specifically bound by and/or transported by another molecule. Preferred ligands include, but are not limited to peptides, nucleic acids,~~ carbohydtares~~ carbohydrates, sugars, hormones, and the like. A ligand and a molecule that it binds form a binding pair, in which each one member is regarded as a ligand in respect to the other member. Specific examples of binding pairs include antibody/antigen, antibody/hapten, enzyme/substrate, enzyme/inhibitor, enzyme/cofactor, binding protein/substrate, carrier protein/substrate, transporter protein/substrate, lectin/carbohydrate, receptor/hormone, receptor/modulator, complementary strands of polynucleotides, protein/nucleic acid repressor(inductor), receptor/virus, *etc.*

Please replace the paragraph [0044] with the following amended paragraph(s):

[0044] The term "detect" refers to detection or quantitative determination.

Please replace the paragraph [0048] with the following amended paragraph(s):

[0048] Figure 2 illustrates the specificity of the CLIA assay. SKBR3 tumor cells were incubated with NTA-liposomes (5 mol. % Ni-NTA-DOGS) and the anti-ErbB2 antibody F5 without a $(His)_6$-tag, or a non-internalizing anti-ErbB2 antibody (C6.5), or no scFv. Alternatively, the F5 scFv containing the $(His)_6$-tag was co-incubated with~~ fluorescenly~~ fluorescently labeled liposomes formulated without the NTA-DOGS lipid. After four hours of internalization, cells were washed with physiological buffered saline containing 1 mM EDTA, lysed in base and the fluorescence read in a microfluorimeter.

Please replace the paragraph [0098] with the following amended paragraph(s):

[0098] Metal chelating lipid conjugates capable of being incorporated into a lipid vesicle are generally described by Wagner, *et al.*, US Pat. No. 4,707,453. Unlike high-stability ~~high stability~~ metal chelates, the present invention, in preferred embodiments, uses chelating lipid conjugates that produce metal complexes of moderate (or low) stability, and typically having fewer coordination sites than the metal, *e.g.* as in NTA- or IDA groups, so that the complex coordination sphere of the metal ion in the complex is incomplete, affording

formation of the metal chelation bond between the metal and the epitope tag of the ligand. Such chelation bonds can be readily dissociated by the action of a commonly used, cell-sparing chelator/metal-binding agent with higher metal-binding strength, such as ethylenediamine tetraacetate (EDTA) ~~of~~ or ~~t~~diethylenetriamine pentaatcetate (DTPA).

Please replace the paragraph [0102] with the following amended paragraph(s):

[0102] Lipids commonly used to form liposomes, such as, di(C_{10}-C_{22}) alkyl-(or alkenyl-) phosphatidylethanolamines, di(C_{10}-C_{22}) alkyl-(or alkenyl-)phosphatidic acids, di(C_{10}-C_{22}) alkyl-(or alkenyl-)phosphatidyl glycerols, di(C_{10}-C_{22}) alkyl-, alkenyl-, alkanoyl, or alkenoyl, ~~lglycerols~~ glycerols, sphingolipids, glycophospholipids, sterols, their derivatives, as well as synthetic lipid "anchors" such as di(C_{10}-C_{22}) alkyl-(or alkenyl-)amines or similar alkanoyl amides are suitable. Lipid-polymer-chelator conjugates are incorporated into lipid matrix of the liposome either before, or after the liposome formation (by co-incubation with pre-formed liposomes), in the amount of 0.1-50 mol% of the liposome-lipid, preferably 0.5-10 mol.%, and most preferably at 0.5-5 mol.% of the liposome lipid. In a particular embodiment, poly(ethylene glycol)-lipid is poly(ethylene glycol)-conjugated DSPE, and a chelation group is NTA.

Please replace the paragraph [0132] with the following amended paragraph(s):

[0132] In certain embodiments this invention provides a composition for delivery of an effector into a cell, which composition comprises (i) a metal-chelating lipid comprising a hydrophobic lipid portion, a hydrophilic polymer linked to said lipid portion, and a chelation group linked to said hydrophilic polymer wherein the chelation group is complexed to a metal ion and binds to an epitope tag, and (ii) a ligand comprising said epitope tag, where the epitope tag comprises a sequence of at least two neighboring histidine residues (a histidine tag), and where effector is associated with said metal-chelating lipid. The tag preferably comprises six neighboring histidine residues (hexahistidine tag). A preferred composition is one where the metal-chelating lipid and the effector are comprised in a liposome. Any effectors and/or ligands described herein are suitable. The effector is for example, a reporter, a cytotoxin, a drug, or a nucleic acid. The ligand is typically a protein, a carbohydrate, a nucleic acid, of a small organic molecule. The ligand may be natural or synthetic. Preferred protein ligands are those that comprise the antigen-binding sequences of an antibody, such as ~~immnoglobulins~~ immunoglobulins and fragments thereof, both naturally and recombinantly produced, including single-chain fragments. The liposome may further comprise a lipid-polymer conjugate, particularly, a lipid-poly(ethylene glycol) conjugate. In the liposome, the

metal-chelating lipid typically constitutes between 0.1 mol% and 50 mol.% , preferably between 0.2 mol.% and 10 mol%. Optionally, the lipid-polymer conjugate (without the metal-chelating group) can be included to up to 20 mol% of the liposome lipid.

Please replace the paragraph [0141] with the following amended paragraph(s):

[0141] Liposomes are prepared from 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC) and cholesterol (6:4 molar ratio) and varying amounts of NTA-DOGS (Avanti Lipids; 0.5-5 mol. % of POPC amount) by lipid film hydration in solution containing 35 mM 8-hydroxypyrene-1,3,5-trisulfonic acid sodium salt (HPTS) (Molecular Probes Inc., Oregon, USA), pH 7.0, adjusted to the osmolality of 280 mmol/kg with NaCl. In some cases, the liposomes were made using 1,2-distearoyl-phosphatidylcholine (DSPC) instead of POPC, and the lipophilic fluorescent labels $DiIC_{18}(3)$-DS and $DiIC1_8(5)$-DS (0.1-1 mol.% of the liposome phospholipid) were used instead of HPTS, with the same results. In these cases, hydration is at 55-60 °C in an aqueous 140 mM NaCl buffered with 5-20 mM 4-(N-2-hydroxyethyl-piperasino)ethylsulfonic acid sodium salt (HEPES) to pH 7.2-7.4. After hydration, liposomes are formed by membrane extrusion through two 0.1 µm polycarbonate membranes (Corning) as described (Kirpotin *et al.* (1997) *Biochemistry* 36: 66-75). Un~~incapsulated~~ encapsulated HPTS was then separated by gel-filtration on a ~~cross linkled~~ cross-linked dextran beads (SEPHADEX G-25) (Pharmacia Amersham, New Jersey, USA) column.

Please replace the paragraph [0149] with the following amended paragraph(s):

[0149] The effect of increasing the liposome concentration in the reaction was investigated using the anti-ErbB2 scFv antibody (F5) or an irrelevant antibody binding a vascular antigen not expressed on SKBR3 cells. The cellular uptake of liposomes was proportional to the concentration of liposomes in the reaction. In the 0-800 µM ~~phosholipid~~ phospholipid range tested, the non-specific antibody did not internalize liposomes above background (Figure 4).

Please replace the paragraph [0157] with the following amended paragraph(s):

[0157] 198 mg (0.0445 mmol) of distearoylphosphatidylethanolaminocarbonyl-poly(ethylene glycol)-propionic acid N-hydroxysuccinimidyl ester (NHS-PEG-DSPE, Shearwater Polymers, Alabama, USA) prepared from poly(ethylene glycol) with mol. weight 3,400 were dissolved in the mixture of 1 mL of anhydrous ethanol and 0.5 ml of anhydrous chloroform, mixed with the solution of 40.8 mg (0.120 mmol) of **I** hyrdobromide in 0.5 mL of anhydrous ethanol and 0.15 mL (1.08 mmol) of triethylamine, and stirred 2 hours at 60°C. The reaction mixture was brought

to dryness and dissolved in 3 ml of 0.14 M aqueous NaCl. The mixture was clarified by centrifugation at 15,500xg for 5 min., and clear supernatant was brought to dryness in vacuum. The residue was dissolved in 2.5 ml of 0.144 M NaCl, pH was adjusted to 6.8 with 1 N NaCl, and 0.12 mL of 1 M $NiSO_4$ were added. The solution was chromatographed on a 13-mL column with cross-linked dextran beads (Sephadex G-75, Pharmacia Amersham, USA) using 0.144 M NaCl as eluent. The fractions appearing at the void volume (total 4 mL) were collected, and dried by lyophilization overnight. The lyophilized cake was extracted with the mixture of 2 ml anhydrous ethanol and 0.2 ml chloroform; the insoluble matter was removed by centrifugation, and the clear solution was brought to dryness in vacuum. The residue was redissolved in 2 ml of ethanol containing 0.1 ml of chloroform, the solution clarified by centrifugation (15.5xg, 5 min), and brought to dryness in vacuum. Yield 92 mg (46% of theory). The bluish solid was soluble in ~~in~~ chloroform-methanol mixture (60:40 by vol.) and in water, giving light-blue solutions. The intended structure was confirmed by PMR.

Please replace the paragraph [0159] with the following amended paragraph(s):

[0159] Liposomes having lipid composition of DSPC, cholesterol, methoxy-poly(ethylene glycol)-DSPE derivative (PEG(2000)-DSPE, PEG mol. weight 2,000; Avanti Polar Lipids, Alabama, USA), and compound **V** (Ni-NTA-PEG-DSPE) in the molar ratio of 3:2:0.05:0.06 were prepared by lipid film hydration and polycarbonate track-etched membrane (0.1 μm, 10 times) extrusion at 55°C in 0.25M aqueous ammonium sulfate. After removal of unencapsulated ammonium sulfate and bringing the liposomes into 5% dextrose, 5 mM morpholinoethanesulfonic acid (MES) buffer, pH 5.5 (adjusted with sodium hydroxide) by gel-chromatography using cross-linked dextran beads (Sephadex G-75, Pharmacia, New Jersey, USA), the liposomes were mixed with 10 mg/ml vinorelbine bitartrate solution USP (GlaxoWellcome, USA) to achieve drug/lipid molar ratio of 5:1 and incubated at 55°C for 30 min. to achieve drug encapsulation. Unencapsulated vinorelbine was removed by gel-chromatography as above. Typically >80% of the drug remained encapsulated into so obtained Ni-NTA-PEG-DSPE-containing liposomes. Control liposomes were made substituting PEG-DSPE for Ni-NTA-PEG-DSPE, and were loaded with vinorelbine in a similar way. Liposomes containing covalently bound 4G7 were prepared by incubating vinorelbine-loaded control liposomes with 4G7 conjugated to an amphipathic linker, maleimido-PEG-DSPE (Papahadjopoulos, *et al.* US Pat. No. 6,210,707). Bovine endothelial cells (BEND-3) expressing vascular endothelial growth factor (VEGF) receptor were incubated (37°C, 6 hours) in the growth medium containing 0.03-90 microgram/mL of the free (*i.e.* non-encapsulated) vinorelbine, or vinorelbine encapsulated in the Ni-NTA-PEG-DSPE liposomes with or without 0.02 mg/mL of the internalizing anti-VEGFR scFv

antibody 4G7 having a hexahistidine tag and a terminal cysteine group. The cells were post-incubated in the growth medium without the drug for another 72 hours, and the viability of the cells was determined by a conventional tetrasolium (MTT) assay. The median cytotoxic dose, i.e. the dose that reduces the cell viability to 50% of non-treated control (IC_{50}), was as follows: free vinorelbine, 0.67 μg/mL; vinorelbine in Ni-NTA-PEG-DSPE liposomes without 4G7 scFv, >100 μg/mL (IC_{50} not reached); control liposomes + 4G7 scFv, >100 μg/mL (IC_{50} not reached); vinorelbine in liposomes with covalently bound 4G7, 2.5 μg/ml; Ni-NTA-PEG-DSPE liposomes + 4G7 scFv, 1.4 μg/mL. Thus, we observed specific delivery of vinorelbine into vascular ~~epitelial~~ epithelial cells by Ni-NTA-PEG-DSPE-containing liposomes coupled to a receptor-specific scFv via a hexahistidine tag.